

**Clinical trial results:****Effect of oral EGb 761® on Brain Glucose Metabolism in Three Groups of Elderly with Memory Complaint, mild Alzheimer's Disease, and Cognitively Normal Elderly. Phase II, randomised, double-blind, parallel groups, placebo-controlled study****Summary**

EudraCT number	2007-005377-63
Trial protocol	FR
Global end of trial date	17 July 2012

Results information

Result version number	v1 (current)
This version publication date	17 April 2016
First version publication date	17 April 2016
Summary attachment (see zip file)	Non-Serious adverse events (Non-Serious adverse events.pdf)

Trial information**Trial identification**

Sponsor protocol code	2-39-00240-134
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65 Quai Georges Gorse, Boulogne Billancourt, Cedex, France, 92100
Public contact	Ipsen Pharma, Medical Director, Neurology, clinical.trials@ipsen.com
Scientific contact	Ipsen Pharma, Medical Director, Neurology, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2012
Global end of trial reached?	Yes
Global end of trial date	17 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of four weeks treatment with EGb761® in comparison to placebo in three groups of elderly : MC, AD and CNE. The primary endpoint will be the change in brain glucose metabolism at M1 versus baseline as measured using 18 FDG-PET.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	17 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	46
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 63 participants were screened of which 49 subjects were randomised to either EGb761 and Placebo treatment groups (double-blind period).

The 49 randomised subjects consisted of three groups of elderly subjects: Cognitively normal elderly (CNE), Memory Complaint (MC) and Alzheimer's Disease (AD).

Period 1

Period 1 title	Double-blind Phase (4 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	EGb761 120 mg

Arm description:

EGb761 120 mg tablet twice a day for 4 weeks (Double-blind phase) for CNE, MC, and AD patients and 17 months (Open phase) for CNE and MC patients

Arm type	Experimental
Investigational medicinal product name	EGb 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All subjects received 4 weeks treatment with either EGb761 (120 mg BID) or placebo in a double blind manner. Since the actual number of subjects enrolled in the AD group was lower than initially anticipated, the AD group was not considered for efficacy variables. Thereafter, CNE and MC subjects received EGb761 during an open 17 month follow up period.

Arm title	Placebo
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Arm description:

Placebo 1 tablet twice a day for 4 weeks CNE, MC, and AD patients

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All subjects were followed for 4 weeks in order to evaluate the efficacy of EGb761, 120 mg BID versus placebo in terms of brain glucose metabolism. Subjects were to take one tablet in the morning and one in the evening. Thereafter, according to the initial diagnosis, only MC and CNE subjects would be followed for 17 months, in an open manner.

Number of subjects in period 1	EGB761 120 mg	Placebo
Started	23	26
CNE	10 ^[1]	13 ^[2]
MC	10 ^[3]	11 ^[4]
AD	3 ^[5]	2 ^[6]
Completed	23	23
Not completed	0	3
Adverse event, non-fatal	-	1
Not specified	-	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Open period was treated with EGB761®. 41 subjects accepted follow-up open period(21 in CNE,20 in MC)

Open period was not proposed to AD subjects.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was an open period, without placebo arm, the number of subject on placebo is 0.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Open period was treated with EGB761®. 41 subjects accepted follow-up open period(21 in CNE,20 in MC)

Open period was not proposed to AD subjects.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was an open period, without placebo arm, the number of subject on placebo is 0.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Open period was treated with EGB761®. 41 subjects accepted follow-up open period(21 in CNE,20 in MC)

Open period was not proposed to AD subjects.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was an open period, without placebo arm, the number of subject on placebo is 0.

Period 2

Period 2 title	Open Phase (17 Months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	EGB761 120 mg
Arm description:	EGB761 120 mg tablet twice a day for 4 weeks (Double-blind phase) for CNE, MC, and AD patients and 17 months (Open phase) for CNE and MC patients
Arm type	Experimental

Investigational medicinal product name	EGB 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All subjects received 4 weeks treatment with either EGB761 (120 mg BID) or placebo in a double blind manner. Since the actual number of subjects enrolled in the AD group was lower than initially anticipated, the AD group was not considered for efficacy variables. Thereafter, CNE and MC subjects received EGB761 during an open 17 month follow up period.

Number of subjects in period 2^[7]	EGB761 120 mg
Started	41
CNE	21 ^[8]
MC	20 ^[9]
AD	0 ^[10]
Completed	31
Not completed	10
Consent withdrawn by subject	2
Adverse event, non-fatal	5
Not otherwise specified	1
Lost to follow-up	2

Notes:

[7] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Open period was treated with EGB761®. 41 subjects accepted follow-up open period(21 in CNE,20 in MC)

Open period was not proposed to AD subjects.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Open period was treated with EGB761®. 41 subjects accepted follow-up open period(21 in CNE,20 in MC)

Open period was not proposed to AD subjects.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Open period was treated with EGB761®. 41 subjects accepted follow-up open period(21 in CNE,20 in MC)

Open period was not proposed to AD subjects.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: In open phase all subjects (only CNE & MC groups) were administered with EGB761 120 mg.

Baseline characteristics

Reporting groups

Reporting group title	EGb761 120 mg
Reporting group description:	EGb761 120 mg tablet twice a day for 4 weeks (Double-blind phase) for CNE, MC, and AD patients and 17 months (Open phase) for CNE and MC patients
Reporting group title	Placebo
Reporting group description:	Placebo 1 tablet twice a day for 4 weeks CNE, MC, and AD patients

Reporting group values	EGb761 120 mg	Placebo	Total
Number of subjects	23	26	49
Age categorical			
Units: Subjects			
From 65-84 years	21	25	46
85 years and over	2	1	3
Age continuous			
Units: years			
arithmetic mean	75.1	76.6	-
standard deviation	± 6.2	± 5.3	-
Gender categorical			
Units: Subjects			
Female	15	17	32
Male	8	9	17
Education			
Level 1: Primary only			
Level 2: School certificate			
Level 3: Completed secondary			
Level 4: University			
Units: Subjects			
Level 1	1	0	1
Level 2	2	5	7
Level 3	3	6	9
Level 4	17	15	32
BMI			
Units: kg/m ²			
arithmetic mean	24.49	25.03	-
standard deviation	± 4.46	± 4.4	-

End points

End points reporting groups

Reporting group title	EGB761 120 mg
Reporting group description: EGB761 120 mg tablet twice a day for 4 weeks (Double-blind phase) for CNE, MC, and AD patients and 17 months (Open phase) for CNE and MC patients	
Reporting group title	Placebo
Reporting group description: Placebo 1 tablet twice a day for 4 weeks CNE, MC, and AD patients	
Reporting group title	EGB761 120 mg
Reporting group description: EGB761 120 mg tablet twice a day for 4 weeks (Double-blind phase) for CNE, MC, and AD patients and 17 months (Open phase) for CNE and MC patients	
Subject analysis set title	EGB761 120 mg (CNE)
Subject analysis set type	Intention-to-treat
Subject analysis set description: EGB761 120 mg tablet twice a day for 4 weeks (Double-blind phase) for CNE patients	
Subject analysis set title	Placebo (CNE)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo 1 tablet twice a day for 4 weeks for CNE patients	
Subject analysis set title	EGB761 120 mg (MC)
Subject analysis set type	Intention-to-treat
Subject analysis set description: EGB761 120 mg tablet twice a day for 4 weeks (Double-blind phase) for MC patients	
Subject analysis set title	Placebo (MC)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo 1 tablet twice a day for 4 weeks for MC patients	
Subject analysis set title	EGB 120 mg (Open Phase - CNE)
Subject analysis set type	Intention-to-treat
Subject analysis set description: EGB761 120 mg tablet twice a day for 17 months (open phase) for CNE patients	
Subject analysis set title	EGB 120 mg (Open Phase - MC)
Subject analysis set type	Intention-to-treat
Subject analysis set description: EGB761 120 mg 17 months (open phase) for MC patients	

Primary: Change in Brain Glucose Metabolism Measured Using 18-Fluorodeoxyglucose Positron Emission Tomography (18FDG-PET)

End point title	Change in Brain Glucose Metabolism Measured Using 18-Fluorodeoxyglucose Positron Emission Tomography (18FDG-PET) ^[1]
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End point description:

Intention to treat (ITT) population: All treated CNE and MC patients

Following statistical parametric mapping (SPM) analyses were performed by the Commissariat à l'Énergie Atomique (CEA):

- The comparison between treatment groups separately for each group of elderly subjects (CNE and MC groups only)
- The comparison between the two groups of elderly subjects (CNE and MC groups only) by treatment group

FDG PET demonstrates reductions in the cerebral glucose metabolism that may occur a few years before the overt clinical manifestation of disease.

$$\text{SUVBSA2} = [\text{Brain radioactivity (Bq/cc)}] / [\text{Injected dose (MBq)/BSA2}] \times [\text{Blood glucose (g/l)}]$$

$$\text{BSA2(m}^2\text{)} = 0.007184 \times \text{Height (cm)}^{0.35} \times \text{weight (kg)}^{0.80}$$

Standardized Uptake Value (SUV) Body Surface Area (BSA)

End point type	Primary
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End point timeframe:

From Baseline (Month 0) to Week 4 (Month 1) - Double blind phase

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses for this endpoint

End point values	EGb761 120 mg (CNE)	Placebo (CNE)	EGb761 120 mg (MC)	Placebo (MC)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	11	10	10
Units: SUVBSA2				
median (full range (min-max))				
Cerebellum	-3.4 (-16.4 to 18.7)	-1.07 (-22.8 to 33.5)	-7.58 (-29.7 to 26.4)	-3.09 (-16.4 to 22.4)
Left cerebral cortex	-8.56 (-14 to 22)	2.25 (-28.9 to 35.9)	0.44 (-36.3 to 35.8)	-0.32 (-33.9 to 30.7)
Left thalamus	-8.46 (-23.3 to 25.1)	-0.06 (-39.6 to 37.4)	-2.09 (-35.2 to 30.1)	-6.19 (-38.9 to 31.2)
Left caudate nucleus	-0.68 (-28 to 29.1)	4.6 (-23.8 to 49.6)	2.16 (-35.8 to 53.4)	3.27 (-51.4 to 25.3)
Left putamen nucleus	-1.91 (-23.7 to 26.3)	-0.19 (-23.5 to 55.8)	2.15 (-46 to 46.2)	-6.2 (-49.1 to 39.8)
Left ventral striatum	1.49 (-53.5 to 19.7)	-7.29 (-30.4 to 67.5)	2.37 (-22.3 to 24.4)	-4.62 (-53.8 to 33.8)
Left globus pallidus	-4.33 (-26.3 to 19.4)	-1.26 (-9.4 to 39.2)	-7.75 (-28.5 to 14)	-8.72 (-24.7 to 26.3)
Right cerebral cortex	-7.49 (-25.3 to 21.4)	0.19 (-29.4 to 38.2)	-7.11 (-32.5 to 35.5)	-6.59 (-36.1 to 31.3)
Right thalamus	-7.4 (-27.3 to 28.7)	-2.05 (-46.6 to 41.5)	-3.87 (-29.9 to 28.1)	-7.72 (-43.4 to 31.1)
Right caudate nucleus	-1.59 (-36.2 to 29.1)	-0.66 (-23.7 to 46)	-9.21 (-34.2 to 40.9)	-6.45 (-41.3 to 16.7)
Right putamen nucleus	-6.31 (-42.9 to 30.8)	-2.73 (-39.1 to 52.8)	-8.84 (-41.7 to 41.8)	5.36 (-50.4 to 25.5)
Right ventral striatum	-7.08 (-23.8 to 32.8)	-0.76 (-43.7 to 41.5)	-8.21 (-27.6 to 65.5)	-0.59 (-51.4 to 27.2)
Right globus pallidus	-2.04 (-21.1 to 17.3)	-1.72 (-22.1 to 40.4)	-5.99 (-23 to 33.7)	-1.24 (-35 to 17.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Brain Glucose Metabolism in the MC and CNE Groups

End point title	Change in Brain Glucose Metabolism in the MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Brain glucose metabolism measured by 18FDG PET

$SUVBSA2 = [\text{Brain radioactivity (Bq/cc)}] / [\text{Injected dose (MBq)/BSA2}] \times [\text{Blood glucose (g/l)}]$

$BSA2(m^2) = 0.007184 \times \text{Height (cm)}^{0.35} \times \text{weight (kg)}^{0.80}$

End point type Secondary

End point timeframe:

From Baseline (Month 0) to Month 18

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	14		
Units: SUVBSA2				
median (full range (min-max))				
Cerebellum	-0.07 (-0.3 to 0.1)	0 (-0.5 to 0.2)		
Left cerebral cortex	-0.06 (-0.3 to 0.1)	-0.08 (-0.5 to 0.1)		
Left thalamus	-0.03 (-0.2 to 0.1)	-0.02 (-0.8 to 0.1)		
Left caudate nucleus	-0.11 (-0.8 to 0.2)	-0.01 (-0.6 to 0.2)		
Left putamen nucleus	0.07 (-0.3 to 0.2)	0 (-0.5 to 0.3)		
Left ventral striatum	-0.05 (-0.5 to 0.3)	-0.09 (-0.5 to 0.1)		
Left globus pallidus	0 (-0.3 to 0.2)	-0.01 (-0.2 to 0.1)		
Right cerebral cortex	-0.07 (-0.3 to 0.1)	-0.06 (-0.3 to 0.1)		
Right thalamus	0.04 (-0.3 to 0.2)	0 (-0.9 to 0.2)		
Right caudate nucleus	0.03 (-0.6 to 0.2)	-0.02 (-0.6 to 0.3)		
Right putamen nucleus	0.04 (-0.5 to 0.2)	0.02 (-0.3 to 0.3)		
Right ventral striatum	0.01 (-0.4 to 0.3)	-0.05 (-0.6 to 0.4)		
Right globus pallidus	0.06 (-0.3 to 0.4)	0.06 (-0.2 to 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Clinical Dementia Rating (CDR) Score in MC and CNE Groups

End point title Change in Cognitive Tests-Clinical Dementia Rating (CDR)

End point description:

ITT population. N=Number of subjects with assessment

CDR is a structured interview to collect information regarding subject's memory in a standard way from both the patient and the helper. Scores are calculated using below scale; q CDR=No dementia (score: 0), q CDR=Very mild dementia (score: 0.5), q CDR=Mild dementia (score: 1), q CDR=Moderate dementia (score: 2) and q CDR=Severe dementia (score: 3).

End point type Secondary

End point timeframe:

From Baseline (Month 0) to Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	18		
Units: CDR overall score				
median (full range (min-max))	0 (0 to 0.5)	0 (-0.5 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Geriatric Depression Scale (GDS) Score in MC and CNE Groups

End point title Change in Cognitive Tests-Geriatric Depression Scale (GDS) Score in MC and CNE Groups

End point description:

ITT population. N=Number of subjects with assessment.

The Geriatric Depression Scale is a self-administered depression scale, which was developed as a basic screening measure for depression in older adults. By "yes" or "no" answers, scores permit to classify patients into groups of "severely depressed" (score of 21 to 30), "moderately depressed" (score of 11 to 20) and "normal" (score of 0 to 10). It takes 10 to 15 minutes to administer.

End point type Secondary

End point timeframe:

From Baseline (Month 0) to Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	17		
Units: GDS Score				
median (full range (min-max))	-2 (-6 to 8)	0 (-5 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Verbal Fluency in MC and CNE Groups

End point title	Change in Cognitive Tests-Verbal Fluency in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Subjects completed a verbal fluency test. Higher scores represent higher levels of verbal fluency. Minimum score=0 and Maximum score= N/A.

Letter fluency: this task consists of enouncing as many words as possible that begin with a given letter of the alphabet. Participants are not allowed to use proper names.

Categorical fluency: in this task participants are asked to list as many words as possible that belong to a given semantic category (e.g. animals, fruits, towns) Each condition foresees 60 sec of word generation time. The score corresponds to the number of words correctly given. The verbal fluency task measures semantic storage and executive retrieval functions.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: Number of good answers				
median (full range (min-max))				
Categorical verbal fluency	-1.5 (-14 to 11)	-2 (-16 to 6)		
Lexical verbal fluency	-1 (-14 to 10)	2 (-18 to 22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Mini Mental Status Examination (MMSE) Score in MC and CNE Groups

End point title	Change in Cognitive Tests-Mini Mental Status Examination (MMSE) Score in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

MMSE is a brief screening instrument used to assess cognitive function in elderly participants. It assesses orientation, memory, attention, ability to name objects, follow verbal and written commands, write a sentence, and copy figures. Total score ranges from 0 to 30, with a lower score indicating greater disease severity.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: MMSE Score				
median (full range (min-max))	0 (-2 to 1)	0 (-6 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Clock Drawing Test Score in MC and CNE Groups

End point title	Change in Cognitive Tests-Clock Drawing Test Score in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Clock drawing test is a visuo-constructive task, where subjects are asked to draw the face of a clock in a pre-drawn circle and then to draw in the arms to denote 16:45 (a quarter to five). The drawing can then be evaluated by a quantitative scoring method, which is based on the degree of completion of the drawing. The scoring system ranges from 0 to 6 with higher scores reflecting a greater number of errors and more impairment.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: Clock drawing test score				
median (full range (min-max))	0 (-3 to 2)	0 (-5 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Cube Drawing Test Score in MC and CNE Groups

End point title	Change in Cognitive Tests-Cube Drawing Test Score in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Cube drawing: Subjects are asked to draw a cube by heart. In case of failure, a model of a cube is given to the subjects to copy.

The score system ranges from 0 (worse score) to 6 (best score). Score calculation is following: 1 point by face with 4 sides, 2 points for each face where each angle should be respected.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: Cube drawing test score				
median (full range (min-max))	0 (-2 to 1)	0 (-4 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests in MC and CNE Groups - Total Immediate Recall and Delayed Recall Scores of the Free and Cued Selective Reminding Test (FCSRT)

End point title	Change in Cognitive Tests in MC and CNE Groups - Total Immediate Recall and Delayed Recall Scores of the Free and Cued Selective Reminding Test (FCSRT)
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End point description:

ITT population. N=Number of subjects with assessment.

Free and Cued Selective Reminding Test (FCSRT) Assessment of verbal episodic memory. By this test performances in free recalls, cued recalls and in a recognition task can be analysed, because the process of encoding is controlled.

Subjects are asked to remember a list of 16 words. Three tasks of free and cued recalls, as well as one recognition task and one delayed recall give the scores.

Total recall is obtained by the addition of cued recalls to free recalls. Maximum score is 48 for immediate: 16 words X 3 corresponding to immediate free recall + immediate cued recall + immediate recognition test.

Maximum score is 64 (better score) when delayed recall : 16 words X 4 . The minimum score is 0 (worse).

End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 9	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: Recall score				
median (full range (min-max))				
Total Immediate Recall Score	1 (-1 to 10)	0 (-10 to 11)		
Total Delayed Recall Score	0 (-4 to 6)	0 (-4 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Age-Adjusted Logical Memory (MEM III) in MC and CNE Groups

End point title	Change in Cognitive Tests-Age-Adjusted Logical Memory (MEM III) in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Subjects are asked to memorize two short stories, one consisting of 24, the other one of 26 information units. After the stories have been read aloud by the investigator, subjects are asked to enounce all items of information they can remember (free recall). Correctly reported items are added for each story. This test applies analytical capacities, as well as auditive and verbal synthesis, working memory and episodic memory.

Score range from 0(worst) to 75 (better).

End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 9	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	17		
Units: Age adjusted score				
median (full range (min-max))	1 (-5 to 6)	-1 (-4 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Age-Adjusted Wechsler Adult Intelligence Scale (WAIS) in MC and CNE Groups

End point title	Change in Cognitive Tests-Age-Adjusted Wechsler Adult Intelligence Scale (WAIS) in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Wechsler Adult Intelligence Scale (WAIS) In this test subjects are asked to say how two seemingly dissimilar items might in fact be similar (14 item couples). This test involves especially abstract thinking and concept capacities.

Cognitive Tests-Age-Adjusted Wechsler Adult Intelligence Scale (WAIS): 19 tests on similarities. The items 1 to 5 are graded from 1 (good) to 0 (bad), and the items 6 to 19 are graded from 2 (good) to 0 (bad). Item 6 and 7 can be repeated. At the end, the worst total score is 0, the best total score is 33.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	18		
Units: Age adjusted score				
median (full range (min-max))	1 (-3 to 5)	1 (-3 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Time to Perform Trail Making Test (TMT) in MC and CNE Groups

End point title	Change in Cognitive Tests-Time to Perform Trail Making Test (TMT) in MC and CNE Groups
-----------------	--

End point description:

ITT population. N=Number of subjects with assessment.

TMT is a neuropsychological test of visual attention and task switching. The task requires a subject to 'connect-the-dots' of 25 consecutive numbers (1,2,3,etc.) on a sheet of paper or computer screen. The goal of the subject is to finish the test as quickly as possible and the time taken to complete the test is used as the primary performance metric (in seconds). The maximum time allowed is 300 seconds. A negative change score indicates improvement.

First, in the TMT A, the subject has to connect numbers increasingly as fast as possible.

The TMT B requires the subject to connect and letters in an alternating pattern (1-A-2-B-3-C, etc.) in as little time as possible.

End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 9	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: seconds				
median (full range (min-max))				
Task A (N=17,18)	2 (-43 to 41)	2.5 (-18 to 31)		
Task B (N=17,16)	0 (-200 to 56)	-5.5 (-57 to 113)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to the DSM IV (Diagnostic of Dementia)

End point title	Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to the DSM IV (Diagnostic of Dementia)
-----------------	--

End point description:

ITT population. N=Number of subjects with assessment.

The Diagnostic and Statistical Manual of Mental Disorders: 4th Edition of the American Psychiatric Association (DSM-IV, 1994) also outlines diagnostic criteria for dementia of the Alzheimer's type that are generally consistent with the NINCDS-ADRDA criteria.

National Institute of Neurological and Communicative Diseases and Stroke / Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA)

End point type	Secondary
End point timeframe:	
At Month 9	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to NINCDS-ADRDA (Diagnostic of Alzheimer's)

End point title	Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to NINCDS-ADRDA (Diagnostic of Alzheimer's)
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End point description:

ITT population. N=Number of subjects with assessment.

The most widely accepted diagnostic criteria for probable AD are those offered by the National Institute of Neurological and Communicative Disorders and Stroke and by the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). These criteria include the presence of dementia established by clinical examination and confirmed by neuropsychological testing. The dementia is described as involving multiple, progressive cognitive deficits in older persons in the absence of disturbances of consciousness, presence of psychoactive substances, or any other medical, neurological, or psychiatric conditions that might in and of themselves account for these progressive deficits.

End point type	Secondary
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End point timeframe:

At Month 9

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-CDR Score in MC and CNE Groups

End point title	Change in Cognitive Tests-CDR Score in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

CDR is a structured interview to collect information regarding subject's memory in a standard way from both the patient and the helper. Scores are calculated using below scale; q CDR=No dementia (score: 0), q CDR=Very mild dementia (score: 0.5), q CDR=Mild dementia (score: 1), q CDR=Moderate

dementia (score: 2) and q CDR=Severe dementia (score: 3)

End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 18	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: CDR overall score				
median (full range (min-max))	0 (0 to 0.5)	0 (-0.5 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-GDS Score in MC and CNE Groups

End point title	Change in Cognitive Tests-GDS Score in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

The Geriatric Depression Scale is a self-administered depression scale, which was developed as a basic screening measure for depression in older adults. By "yes" or "no" answers, scores permit to classify patients into groups of "severely depressed" (score of 21 to 30), "moderately depressed" (score of 11 to 20) and "normal" (score of 0 to 10). It takes 10 to 15 minutes to administer.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 18

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: GDS Score				
median (full range (min-max))	1 (-7 to 17)	0.5 (-5 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Verbal Fluency in MC and CNE Groups

End point title	Change in Cognitive Tests-Verbal Fluency in MC and CNE Groups
End point description:	
ITT population. N=Number of subjects with assessment.	
Subjects completed a verbal fluency test. Higher scores represent higher levels of verbal fluency. Minimum score=0 and Maximum score= N/A.	
Letter fluency: this task consists of enouncing as many words as possible that begin with a given letter of the alphabet. Participants are not allowed to use proper names.	
Categorical fluency: in this task participants are asked to list as many words as possible that belong to a given semantic category (e.g. animals, fruits, towns) Each condition foresees 60 sec of word generation time. The score corresponds to the number of words correctly given. The verbal fluency task measures semantic storage and executive retrieval functions.	
End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 18	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: Number of good answers				
median (full range (min-max))				
categorical verbal fluency	-1 (-18 to 20)	1 (-9 to 10)		
lexical verbal fluency	-1 (-16 to 18)	1.5 (-7 to 22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-MMSE Score in MC and CNE Groups

End point title	Change in Cognitive Tests-MMSE Score in MC and CNE Groups
End point description:	
ITT population. N=Number of subjects with assessment.	
MMSE is a brief screening instrument used to assess cognitive function in elderly participants. It assesses orientation, memory, attention, ability to name objects, follow verbal and written commands, write a sentence, and copy figures. Total score ranges from 0 to 30, with a lower score indicating greater disease severity.	
End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 18	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: MMSE Score				
median (full range (min-max))	0 (-4 to 2)	0 (-5 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Clock Drawing Test Score in MC and CNE Groups

End point title	Change in Cognitive Tests-Clock Drawing Test Score in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Clock drawing test is a visuo-constructive task, where subjects are asked to draw the face of a clock in a pre-drawn circle and then to draw in the arms to denote 16:45 (a quarter to five). The drawing can then be evaluated by a quantitative scoring method, which is based on the degree of completion of the drawing. The scoring system ranges from 0 to 6 with higher scores reflecting a greater number of errors and more impairment.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 18

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: Clock drawing test score				
median (full range (min-max))	0 (-4 to 1)	0 (-3 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Cube Drawing Test Score in MC and CNE Groups

End point title	Change in Cognitive Tests-Cube Drawing Test Score in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Cube drawing: Subjects are asked to draw a cube by heart. In case of failure, a model of a cube is given

to the subjects to copy.

The score system ranges from 0 (worse score) to 6 (best score). Score calculation is following: 1 point by face with 4 sides, 2 points for each face where each angle should be respected.

End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 18	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: Cube drawing test score				
median (full range (min-max))	0 (-6 to 2)	0 (-4 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests in MC and CNE Groups - Total Immediate Recall and Delayed Recall Scores of FCSRT

End point title	Change in Cognitive Tests in MC and CNE Groups - Total Immediate Recall and Delayed Recall Scores of FCSRT
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End point description:

ITT population. N=Number of subjects with assessment.

Free and Cued Selective Reminding Test (FCSRT) Assessment of verbal episodic memory. By this test performances in free recalls, cued recalls and in a recognition task can be analysed, because the process of encoding is controlled.

Subjects are asked to remember a list of 16 words. Three tasks of free and cued recalls, as well as one recognition task and one delayed recall give the scores.

Total recall is obtained by the addition of cued recalls to free recalls. Maximum score is 48 for immediate: 16 words X 3 corresponding to immediate free recall + immediate cued recall + immediate recognition test.

Maximum score is 64 (better score) when delayed recall : 16 words X 4 . The minimum score is 0 (worse).

End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 18	

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: Recall score				
median (full range (min-max))				
Total Immediate Recall Score of FCSRT	2 (-3 to 16)	1.5 (-4 to 8)		
Total Delayed Recall Score of FCSRT	0 (-6 to 6)	0 (-2 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Age-Adjusted Logical Memory (MEM III) in MC and CNE Groups

End point title	Change in Cognitive Tests-Age-Adjusted Logical Memory (MEM III) in MC and CNE Groups
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End point description:

ITT population. N=Number of subjects with assessment.

Subjects are asked to memorize two short stories, one consisting of 24, the other one of 26 information units. After the stories have been read aloud by the investigator, subjects are asked to enounce all items of information they can remember (free recall). Correctly reported items are added for each story. This test applies analytical capacities, as well as auditive and verbal synthesis, working memory and episodic memory.

Score range from 0(worst) to 75 (better).

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 18

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	11		
Units: Age adjusted score				
median (full range (min-max))	0 (-4 to 7)	0 (-4 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Age-Adjusted WAIS in MC and CNE Groups

End point title	Change in Cognitive Tests-Age-Adjusted WAIS in MC and CNE Groups
-----------------	--

End point description:

ITT population. N=Number of subjects with assessment.

Wechsler Adult Intelligence Scale (WAIS) In this test subjects are asked to say how two seemingly dissimilar items might in fact be similar (14 item couples). This test involves especially abstract thinking and concept capacities.

Cognitive Tests-Age-Adjusted Wechsler Adult Intelligence Scale (WAIS): 19 tests on similarities. The items 1 to 5 are graded from 1 (good) to 0 (bad), and the items 6 to 19 are graded from 2 (good) to 0 (bad). Item 6 and 7 can be repeated. At the end, the worst total score is 0, the best total score is 33.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 18

End point values	EGB 120 mg (Open Phase - CNE)	EGB 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	12		
Units: Age adjusted score				
median (full range (min-max))	1 (-3 to 4)	1.5 (-2 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cognitive Tests-Time to Perform TMT in MC and CNE Groups

End point title	Change in Cognitive Tests-Time to Perform TMT in MC and CNE Groups
-----------------	--

End point description:

ITT population. N=Number of subjects with assessment.

TMT is a neuropsychological test of visual attention and task switching. The task requires a subject to 'connect-the-dots' of 25 consecutive numbers (1,2,3,etc.) on a sheet of paper or computer screen. The goal of the subject is to finish the test as quickly as possible and the time taken to complete the test is used as the primary performance metric (in seconds). The maximum time allowed is 300 seconds. A negative change score indicates improvement.

First, in the TMT A, the subject has to connect numbers increasingly as fast as possible. The TMT B requires the subject to connect and letters in an alternating pattern (1-A-2-B-3-C, etc.) in as little time as possible.

End point type	Secondary
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End point timeframe:

From Baseline (Month 0) to Month 18

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: Seconds				
median (full range (min-max))				
Task A (N=18,12)	-3 (-59 to 8)	-1 (-31 to 29)		
Task B (N=18,11)	-4.5 (-213 to 29)	-9 (-76 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to the DSM IV (Diagnostic of Dementia)

End point title	Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to the DSM IV (Diagnostic of Dementia)
-----------------	--

End point description:

ITT population. N=Number of subjects with assessment.

The Diagnostic and Statistical Manual of Mental Disorders: 4th Edition of the American Psychiatric Association (DSM-IV, 1994) also outlines diagnostic criteria for dementia of the Alzheimer's type that are generally consistent with the NINCDS-ADRDA criteria.

End point type	Secondary
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End point timeframe:

At Month 18

End point values	Egb 120 mg (Open Phase - CNE)	Egb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to NINCDS-ADRDA (Diagnostic of Alzheimer's)

End point title	Number of Subjects Conversion to Alzheimer's Dementia Diagnosed According to NINCDS-ADRDA (Diagnostic of Alzheimer's)
-----------------	---

End point description:

ITT population. N=Number of subjects with assessment.

The most widely accepted diagnostic criteria for probable AD are those offered by the National Institute of Neurological and Communicative Disorders and Stroke and by the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). These criteria include the presence of dementia established by clinical examination and confirmed by neuropsychological testing. The dementia is described as involving multiple, progressive cognitive deficits in older persons in the absence of disturbances of consciousness, presence of psychoactive substances, or any other medical, neurological, or psychiatric conditions that might in and of themselves account for these progressive deficits.

End point type	Secondary
End point timeframe:	
At Month 18	

End point values	EgB 120 mg (Open Phase - CNE)	EgB 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Adverse Events (AEs)

End point title	Incidence of Adverse Events (AEs)
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End point description:

Safety population. CNE patients withdrew during the double-blind phase and were also not included in the safety population for open phase (17 months).

The relationship of an adverse event to the study medication will be classified according to the following criteria:

Related : reports including good reasons and sufficient information (e.g. temporal relationship, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with the study drug in the sense that it is plausible, conceivable, or likely

Not related: reports including good reasons and sufficient information (e.g. no temporal relationship and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the study drug.

End point type	Secondary
End point timeframe:	
Up to Month 18	

End point values	EgB761 120 mg	Placebo	EgB761 120 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	26	41	
Units: Participants				
Any Adverse Events	5	9	25	
Any Treatment Emergent	5	8	25	

Intensity of Severe Treatment Emergent AEs (TEAEs)	1	0	6	
Intensity of moderate TEAEs	2	4	14	
Intensity of mild TEAEs	4	5	20	
Causality of Related TEAEs	1	2	3	
Causality of Non Related TEAEs	4	6	25	
Causality and Intensity	0	0	0	
At least one related & severe	0	0	0	
At least one related & moderate	0	1	1	
At least one related & mild	1	2	2	
At least one not related & severe	1	0	6	
At least one not related & moderate	2	3	14	
At least one not related & mild	3	3	20	
TEAEs leading to withdrawal	1	2	4	
TEAES Leading to Death	0	0	0	
Serious AEs (SAEs)	1	0	6	
Non SAEs	5	9	23	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Brain Morphology in the MC and CNE Groups as Determined by the Change in Voxel Size

End point title	Change in Brain Morphology in the MC and CNE Groups as Determined by the Change in Voxel Size
End point description:	
ITT population.	
Evolution of brain morphology (degree of cortical atrophy) after 18 months with EGb761, using MRI voxel based morphometry	
End point type	Secondary
End point timeframe:	
From Baseline (Month 0) to Month 18	

End point values	EGb 120 mg (Open Phase - CNE)	EGb 120 mg (Open Phase - MC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: mm ³				
median (full range (min-max))				
Cerebellum	6454 (-42470 to 30372)	6168.5 (-38855.2 to 65345)		
Left cerebral cortex	5765.5 (-52347 to 97071)	32428 (-103527 to 88300)		
Left thalamus	145.2 (-418.9 to 1023.1)	24.57 (-794.8 to 780.4)		

Left caudate nucleus	154.68 (-387.3 to 1105.3)	140.97 (-827.2 to 1384)		
Left putamen nucleus	-17.14 (-346.4 to 676.4)	4 (-842.6 to 481)		
Left ventral striatum	65.26 (-99 to 157.6)	81.56 (-57.4 to 236.4)		
Left globus pallidus	104.75 (-86.2 to 380.4)	50.66 (-208.7 to 431.8)		
Right cerebral cortex	5853 (-40148 to 103200)	38955.5 (-102169 to 97667)		
Right thalamus	144.83 (-715.7 to 669.6)	14.9 (-570.1 to 755.1)		
Right caudate nucleus	228.74 (-274.2 to 519.6)	303.66 (-223.5 to 1084.4)		
Right putamen nucleus	8.36 (-229.6 to 663.8)	-78.94 (-520.5 to 343.9)		
Right ventral striatum	65.15 (-5.5 to 198.8)	70.85 (-13 to 287.7)		
Right globus pallidus	84.68 (-293 to 312.6)	64.82 (-119.3 to 318.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Up to month 18 follow up

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	EGB761 120 mg (Double-blind)
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Reporting group description:

EGB761 120 mg tablet twice a day for 4 weeks (double-blind phase) for CNE, MC, and AD patients

Reporting group title	Placebo (Double-blind Phase)
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Reporting group description:

Placebo 1 tablet twice a day for 4 weeks (double-blind phase) for CNE, MC, and AD patients

Reporting group title	EGB761 120 mg (Open Phase)
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Reporting group description:

EGB761 120 mg tablet twice a day for 17 months (open phase) for MC and CNE patients

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Patients reporting Non Serious AE by Primary System Organ Class and Preferred term has been attached as an appendix, Since there are no occurrence details available.

Serious adverse events	EGB761 120 mg (Double-blind)	Placebo (Double-blind Phase)	EGB761 120 mg (Open Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	6 / 41 (14.63%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Subclavian artery stenosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	EGB761 120 mg (Double-blind)	Placebo (Double-blind Phase)	EGB761 120 mg (Open Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	0 / 41 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2009	Amendment: 1 <ul style="list-style-type: none">• Addition of investigational sites (multicentre instead of monocentre study)• Change address and name of Beaufour Ipsen Pharma• Change of Ipsen team and PV contacts (due to transfer from Operations France to Drug Development)• Plan for Interim analysis to be added• Correction of scoring for the Clock drawing test and scoring instructions to be added• Correction of number of consent forms to be signed off by the subject• Modification of method of PET scan (same camera to be used for all examinations of a subject)
28 August 2009	Amendment: 2 <ul style="list-style-type: none">• Change of eligibility criterion related to age of subject• Clarification concerning the status (forbidden or authorized) and the way of use (stability definition) of antidepressants/anxiolytics/sedative concomitant medications• Clarification of the direction of IMP use• Definition of "not assessable subject" and procedure of replacement• Clarification of the PET scan procedure (fasting status and blood glucose monitoring before the acquisition and procedure to be followed in case of high blood glucose detected at CEA before performing the imaging)• Questions of GDS scale were modified to match exactly the ones written in the CRF

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported